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THE BACTERIOLOGY OF ACUTE EPIDEMIC RESPIRATORY INFECTIONS COMMONLY CALLED INFLUENZA *

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Aside from a few isolated observations on previous outbreaks of acute epidemic respiratory infections, the most important bacteriologic work on these diseases was done during the great pandemic of 1889-92. The voluminous literature that accrued from these investigations has been carefully reviewed by Finkler,[1] Leichtenstern,[2] and others. Nothwithstanding the great amount of work done during this period, no observer proved that one species of bacteria was of primary importance in the causation of these diseases. The larger group of investigators working during 1890, including Weichselbaum,[3] Babes,[4] Beim,[5] Ribbert,[6] Prior,[7] and Finkler[8] in Germany and Austria, Bouchard,[9] Gaucher,[10] Vaillard,[11] See and Bordas,[12] and Saccoud[13] in France, and many others in widely separated localities, found streptococci and pneumococci in the sputum and postmortem material from the cases of influenza. These findings by different workers in various parts of the world during the early part of the great pandemic of 1890 led to the view that the epidemic respiratory infections were streptococcal or streptococco-pneumococcal in character. In 1890, however, Pfeiffer[14] announced the finding of small gram-negative bacilli in great numbers in stained smears of material from cases of influenza, and in his classic article[15] a short time later, he described B. influenzae as the primary etiologic factor in epidemic acute respiratory infections. Pfeiffer's findings were confirmed by Kitasato,[16] Canon,[17] Pfuhl,[18] Pfeiffer and Beck,[19] and others, and his contention that this organism was the causative factor in these epidemic diseases gained almost universal acceptance at this time. The previously

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[1] 20th Century Practice of Modern Medical Science, 1898, 15, p. 3.

[2] Nothnagel's Encyclopedia of Practical Medicine (Am. edition), 1905, p. 523.

[3] Wien. klin. Wchnschr., 1890, 3, pp. 104, 123, 145, 163, 186.

[4] Centralbl. f. Bakteriol., 1890, 7, pp. 233, 460, 496, 533, 561, 598.

[5] Ztschr. f. klin. Med., 1890, 17, p. 545.

[6] Deutsch. med. Wchnschr., 1890, 16, pp. 61, 301.

[7] München. med. Wchnschr., 1890, 37, p. 233.

[8] Deutsch. med. Wchnschr., 1890, 16, p. 84.

[9] Sem. méd., 1890, 10, p. 35.

[10] Ibid., p. 93.

[11] Ibid., pp. 39, 54.

[12] Compt. rend. de l'Acad. des sc. de Paris, 1890, 110, p. 197.

[13] Sem. méd., 1890, 10, p. 51.

[14] Deutsch. med. Wchnschr., 1890, 18, p. 28.

[15] Ztschr. f. Hyg. u. Infektionskr., 1893, 13, p. 357.

[16] Deutsch. med. Wchnschr., 1892, 18, p. 28.

[17] Ibid., 1892, 18, p. 28.

[18] Centralbl. f. Bakteriol., 1892, 11, p. 397.

[19] Deutsch. med. Wchnschr., 1893, 19, p. 816.

described pathogenic microorganisms — streptococci and pneumococci — were henceforth considered as secondary invaders.

Pfeiffer and his associates isolated influenza bacilli from the sputum and bronchial mucus before death and from the lungs and bronchial mucosa after death of patients suffering from influenza. No observer except Canon[17] has satisfactorily demonstrated influenza bacilli in the blood of persons sick with the disease and Pfeiffer favored the view that influenza was a local infection only, an invasion of the blood by the bacilli not occurring under ordinary circumstances. Experiments designed to produce the disease in animals, including mice, rats, guinea-pigs, rabbits, swine, dogs, and cats, were uniformly negative. In monkeys in a few instances very slight general reactions followed the inoculations, which Pfeiffer considered significant. The characteristic lesions, however, were never found in these animals and when death occurred the cause was probably toxic in nature. The animal experiments of Klein,[20] Kruse,[21] and others, yielded negative results. The failure to demonstrate influenza bacilli in the blood of patients suffering from the disease, and the failure to reproduce the disease in animals, left Pfeiffer's conclusions open to criticism and subsequent bacteriologic results have failed to yield proof of his contentions.

In recent years von Jaksch,[22] Sacquepee,[23] Kleinberger,[24] Bezançon and Israels de Jong,[25] Lord,[26] Davis,[27] and others, in studies of isolated epidemics of influenza have failed to find influenza bacilli with any degree of regularity, but have found streptococci, pneumococci, and other organisms in predominating numbers. Furthermore, during attacks of various acute infectious diseases influenza bacilli have been observed in the mouth as common associates with other bacteria. Thus Elmassian,[28] Davis,[29] Jochmann,[30] and others have found these organisms in the sputum in lobar pneumonia, bronchopneumonia, chronic bronchitis, tuberculosis, whooping cough, measles, and many other diseases. Hence, tho Pfeiffer's work is a classic piece of bacteriologic investigation, his conclusions pertaining to the pathogenic importance of the influenza bacillus are shown by the foregoing observations to have been unwarranted. This microorganism more likely is a common inhabitant of the upper respiratory tract in a great number of acute infectious diseases and except in influenzal meningitis, is of little etiologic significance.

During the winter of 1915-16 a widespread epidemic of acute respiratory infections occurred in the United States which resembled in every detail epidemic influenza. The outbreak was at its height during December, 1915, and January, 1916, and the general mortality of the country was greatly increased. This disease, different from the common acute rhinitis, can be described as an acute erysipelatous inflammation of the mucosa of the upper respiratory passages or of the intestinal tract, with frequent complications and sequelae that often endangered the life of the individual. Because of the unsettled state of our knowledge of the etiology of such diseases and because of their great importance from the standpoint of public health it was thought advisable to study the bacteriology of this epidemic as it occurred in Chicago. The results of this work, partially detailed in a preliminary report,[31] form the basis of this communication.

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[20] Ann. Rep. of the Med. Officer of the Local Govt. Board, London, 1891-92.

[21] Deutsch. med. Wchnschr., 1894, 20, p. 513.

[22] Berl. klin. Wchnschr., 1899, 36, p. 425.

[23] Arch. de méd. expér. et d'anat. path., 1901, 13, p. 562.

[24] Deutsch. med. Wchnschr., 1905, 36, p. 575.

[25] Reviewed in Bull. de l'Inst. Pasteur, 1905, 3, p. 372.

[26] Publ. Mass. Gen. Hosp., 1908-09, 2, p. 715.

[27] Jour. Am. Med. Assn., 1915, 64, p. 1814.

[28] Ann. de l'Inst. Pasteur, 1899, 13, p. 621.

[29] Jour. Am. Med. Assn., 1907, 48, p. 1563; 1915, 64, p. 1814; Jour. Infect. Dis., 1913, 12, p. 386.

[30] Lubarsch u. Ostertag Ergebnisse der Allg. Path., 1909, 13 (Abt. 1), p. 107.

TECHNIC

Cultures were made of material from the upper respiratory passages and the blood of patients at various times during the course of the infection. The material from the nose, throat, and pharynx was collected in sterile containers and washed thoroughly through several changes of sterile normal salt solution. Cover-glass preparations of the fresh material were stained for ordinary bacteria and tubercle bacilli. Aerobic and anaerobic cultures were made on human-blood agar, ascites dextrose broth, ascites dextrose agar, and Loeffler's serum media and incubated at 35-37 C. for 1-14 days. Also in many instances sputum cultures were made by the intraperitoneal inoculation of mice with suspensions of fresh sputum. For blood cultures the blood was drawn from the median basilic vein, and various amounts of whole blood were added to plain agar, plain broth (0.7% acid to phenolthalein), ascites dextrose agar, and ascites dextrose broth. All cultures were allowed to incubate 14 days before they were discarded. The bacteria were identified by the usual bacteriologic methods. The virulence of the various strains of streptococci was determined in a number of instances. For these tests young rabbits were used and varying doses of a 24-hour broth culture of the streptococcus were injected intravenously. The biologic groups of the pneumococci isolated in this work were determined by agglutination tests with the specific sera of Groups I and II.

In the filtration experiments Berkefeld filters of the 'N' type and porcelain filters of the Maussen type were used. The nasal discharge or sputum was macerated in a small amount of sterile salt solution before filtering. Cultures of the filtrates were made in ascites fluid containing a sterile piece of rabbit kidney, as well as on the media previously described for cultures of the original material.

Bacteriologic examination has been made of the sputum, nasal discharge, and pharyngeal mucus from 61 cases of acute epidemic respiratory infection during the acute stage of the disease, and the results are tabulated in Table 1. In 46 instances a virulent hemolytic streptococcus was isolated from this material and in 6 of these this organism was found in pure culture. In 30 cases a green-producing streptococcus was obtained, but only once in pure culture. Pneumococci were isolated in 30 instances, in 4 of which the cultures were pure. The influenza bacillus was found in only 1 instance, and then in mixed culture with a hemolytic streptococcus. In previous work it had been observed that mouse-inoculation of cultures of pneumonic sputum occasionally yielded influenza bacilli as well as pneumococci. This method of culture was also used in 22 instances, with uniformly negative results as far as influenza bacilli were concerned; the findings in every instance corresponded very closely with those of the other cultural methods. Staphylococci were found in 51 instances and many of the strains were hemolytic. Other organisms occasionally found in the aerobic cultures were Micrococcus catarrhalis, B. pneumoniae, and various types of diphtheroid bacilli. Anaerobic cultures usually yielded B. fusiformis, Staphylococcus albus, and diphtheroid bacilli. Green-producing streptococci were also observed in many of the anaerobic cultures, and in one instance an organism similar in morphology and cultural characteristics to B. rhinitis described by Tunnicliff[32] was found in the nasal discharge. In 9 cases blood cultures were made during the height of the disease. Four of these were positive, 3 yielding hemolytic streptococci and 1, pneumococci in pure culture. The cultures from the nasal discharge, during the first 2 or 3 days of the disease, were often negative, while those from the pharynx and throat yielded hemolytic streptococci in predominating numbers. After the second or third day, however, hemolytic streptococci were usually found in the nasal discharge also. Pneumococci were found in the nasal discharge only twice.

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[31] Mathers, Jour. Am. Med. Assn., 1916, 66, p. 30.

TABLE 1

THE BACTERIOLOGIC FINDINGS IN 61 CASES OF ACUTE EPIDEMIC RESPIRATORY INFECTION

Organism	Number of Pure Cultures	Number of Mixed Cultures	Total Number of Cases	Percentage of Total Number of Cases
Hemolytic streptococcus	6	40	46	75.4
S. viridans	1	29	30	49.1
Pneumococcus	4	26	30	49.1
B. influenzae	0	1	1	1.6
M. catarrhalis	0	6	6	9.8
B. pneumoniae	0	1	1	1.6
S. albus	0	51	51	83.6

In 3 instances cultures were made of filtrates of the nasal discharge and sputum during the first 3 days of the disease. Both Berkefeld 'N' filters and Maussen porcelain filters were used. All cultures of filtrates were negative. In cultures on anaerobic ascites-fluid tissue media, after 3-5 days, there appeared a fine turbidity around the tissue, but similar changes appeared in the control tubes and probably represented modifications in the media caused by changes in the tissue. No living bacteria or virus could be demonstrated.

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[32] Jour. Infect. Dis., 1913, 13, p. 283; 1915, 16, p. 493.

In 46 instances a hemolytic streptococcus was found to be the predominating organism in the nasal discharge and sputum of these cases of acute epidemic respiratory infection. In 3 instances it was found in the blood stream in pure culture. The cultural characteristics of the different strains were very similar. On standard blood-agar plates (1 c.c. human blood to 9 c.c. of plain agar), the colonies were small, slightly moist, grayish-white, and surrounded by a sharply defined clear zone of hemolysis, 1-3 mm. in diameter. Growth in ascites dextrose broth was marked, a coarse turbidity and granular sediment appearing in the media after 18-24 hours. In plain broth the growth was scant, and litmus milk was acidified and usually coagulated. Dextrose, saccharose, lactose, and salicin were the most common carbohydrates to be changed. A few strains fermented raffinose and a few mannite, but in no instance was inulin fermented. The virulence for rabbits of 16 strains of the hemolytic streptococcus was studied, and it was found that 1 c.c. of a 24-hour plain-broth culture usually produced arthritis and death in 3-21 days. Morphologically, these hemolytic streptococci varied somewhat, but usually they were medium-sized, round or oval, and gram-positive, growing in pairs and short chains in liquid media. In no instance were capsules demonstrable.

The streptococci were usually found early in the course of the disease, and if no complications appeared they decreased in number or disappeared with the decline of the infection. Cultures from 7 cases made 10 days to 3 weeks after the onset of the disease yielded virulent hemolytic streptoccocci only once. Green-producing streptococci were the predominating organisms late in the course in all these cases.

In 30 cases green-producing streptococci were isolated from the nose and throat. These grew on standard blood-agar plates as small round greenish colonies surrounded by a narrow green halo. Morphologically, they were medium-sized, oval or oblong, gram-positive, and arranged in pairs and short chains. The different strains acidified litmus milk in varying degrees, grew sparingly in plain broth, and fermented dextrose, saccharose, lactose, and salicin usually, but variations were noted in mannite, inulin, and raffinose. The virulence for rabbits was tested in 6 instances and all the strains were found to be of very low virulence.

Pneumococci were also isolated in 30 instances from the nose and throat in these cases, and once from the blood stream. The pneumococci were often atypical in their cultural characteristics. Their biologic reactions have been tabulated in Table 2. They were found to belong usually to Group I or Group IV. The organisms of Group IV predominated, but not to such an extent as to allow any important deductions, for these two types were predominant in the lobar pneumonias occurring in Chicago during the winter of 1915-16. Group I, however, exceeded Group IV in the typical pneumonias, a condition just the reverse of that found in the acute respiratory infections (Table 2).

TABLE 2

THE BIOLOGIC CLASSIFICATION OF THE DIFFERENT STRAINS OF PNEUMOCOCCI FOUND IN THE EPIDEMIC RESPIRATORY INFECTION AND LOBAR PNEUMONIA DURING THE WINTER OF 1915-16

Group	Epidemic Respiratory Infection		Lobar Pneumonia	
	Number of Cases	Percentage of Total	Number of Cases	Percentage of Total
I	10	33.3	14	50.0
II	6	20.0	5	17.8
III	1	3.3	1	3.5
IV	13	43.4	8	28.7

Of the other organisms found in these cultures little need be said. The strain of influenza bacilli and the strains of Micrococcus catarrhalis were typical culturally and morphologically. Many of the staphylococcus strains were hemolytic when first isolated.

In 3 cases the opsonins, agglutinins, and complement-fixing bodies were studied at various stages of the disease. In 2 instances there was a marked increase in the opsonins from the 6th to the 8th day of the infection for the four strains of virulent hemolytic streptococcus tested. There was no demonstrable increase in the agglutinins or complement-fixing bodies in either of these cases. The opsonins also rapidly declined with the recovery of the patient.

The importance of these results from the standpoint of the etiology and pathology of acute epidemic respiratory diseases may be discussed briefly. The clinical and pathologic characteristics of influenza are suggestive of a streptococcic infection. Inflammation of the mucosa of the upper respiratory tract simulating erysipelas in its appearance and mode of spreading, general lymph-node enlargement, the marked tendency to attack the serous surfaces of the body, as well as the acute course, marked prostration and characteristic complications, are all stigmata of a streptococcic disease. In this work hemolytic streptococci were the significant finding in most instances. These streptococci were markedly hemolytic and highly virulent for rabbits, resembling in every detail the streptococcus associated with scarlet fever and epidemic sore throat as described by Davis[33] and others. This organism has been called the beta type of hemolytic streptococcus by Smith and Brown.[34] These virulent organisms are rarely found in the mouths of normal individuals, but are commonly associated with acute infectious diseases in which there are acute inflammatory processes in the upper respiratory tract. Moreover, it is a striking fact that during this epidemic the incidence of other acute infectious diseases, especially scarlet fever and measles, was greatly increased and atypical exanthematous complications were very commonly observed. Also many cases were very similar in every way to epidemic tonsillitis. Such occurrences strongly suggest the possibility of a close relation between epidemic respiratory infections, scarlet fever, and epidemic sore throat. Altho Streptococcus viridans and the pneumococcus must be mentioned as possible etiologic factors in the infection, their similarity to the organisms normally present in the mouth favors the inference that they are of secondary importance. It seems more probable that the etiologic factor was a virulent hemolytic streptococcus. At least it is certain that the influenza bacillus was not of any etiologic significance in the epidemic of acute respiratory infections occurring in Chicago during the winter of 1915-16.

CONCLUSIONS

During the winter of 1915-16 an epidemic of acute respiratory infection occurred in Chicago which closely resembled in its clinicoanatomical manifestations and epidemiology so-called true influenza as it appeared in 1889-92.

In a bacteriologic study of material from 61 cases of this disease the influenza bacillus was found in only 1 instance and then in small numbers. On the other hand, virulent hemolytic streptococci similar in cultural characteristics and virulence to the streptococcus commonly associated with epidemic sore throat and scarlet fever were found in the nose, throat, and pharynx in 46 and in the blood in 3 cases of this epidemic disease.

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[33] Jour. Am. Med. Assn., 1912, 58, p. 1852.

[34] Jour. Med. Research, 1914, 31, p. 455.

Streptococcus viridans and the pneumococcus were each found in 30 instances, these organisms in virulence and biologic characters closely resembling the organisms found in the normal mouth.

The predominance in the discharges from the nose, throat, and pharynx of patients suffering from the epidemic respiratory infection of a virulent hemolytic streptococcus not usually found in the normal mouth, the absence of the influenza bacillus, and the character of the associated pathologic changes suggest that this disease was caused by a virulent hemolytic streptococcus.